Initial comments.

The Examiners rejections are premised on a reading of the prior art in which he characterizes the nuclear proteins fos and jun as "a nuclear receptor ligand" and a "cognate rector for a nuclear transcription factor ligand." Applicants first note that the Examiner's usage is at variance with common usage in the art. Fos and jun **are not** regarded as **receptors** for a nuclear transcription factor ligand.

The Examiner has provided no objective evidence to support his assertion that jun and fos are cognate receptors for a nuclear transcription factor ligand, nor has he identified which (fos or jun) would be regarded by those of skill in the art as a **receptor** (If one is the receptor, the other most be the ligand. Both cannot be the receptor.) Lacking any objective evidence, Applicants understand the Examiner's position to be based on personal knowledge and belief. Accordingly, should the Examiner wish to maintain this position, **Applicants request the Examiner to provide an affidavit to this effect as required by 37 C.F.R. 1.107 (see M.P.E.P. 2144.03).**

Nevertheless, for the purpose of clarity, Applicants have amended claim 1 to expressly recite:

> a) providing a first cell comprising:
> an estrogen receptor;
> a cognate receptor for said nuclear transcription factor ligand;
> fos;
> jun; and
> a promoter comprising an AP-1 site [which]that regulates expression of a first reporter gene;

In view of this amendment it is clear that the "cognate receptor for said nuclear transcription factor ligand" and the "nuclear transcription factor ligand" are not fos and jun.

Obviousness-type double patenting.

The rejection of claims 1-13 are under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-27 of U.S. Patent 5,723,291 was maintained. Applicants respectfully traverse.

The presently pending claims incorporate a limitations not recited in the claims of the '291 patent. In particular, presently pending claim 1 recites:

a) providing a first cell comprising:
an estrogen receptor;
a cognate receptor for said nuclear transcription factor ligand;
fos;
jun; and
a promoter comprising an AP-1 site that regulates expression of a first reporter gene;
b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and
c) detecting expression of said first reporter gene, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, **indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site**

while claim 1 of the '291 patent provides:

a) providing a cell comprising AP1 proteins, an estrogen receptor, and a construct comprising a promoter comprising an AP1 site which regulates expression of a reporter gene;

and

c) detecting the expression of said reporter gene wherein enhanced expression of said reporter gene indicates that said test compound has agonistic estrogenic activity mediated through an indirect estrogen response.

The Examiner has failed to articulate with particularity a teaching or suggestion of the presently claimed method. The Examiner has offered no indication where claims 1-27 of the '291 patent teach or suggest a cognate receptor for a nuclear transcription factor in addition to the fos and jun as recited in element "a" of presently pending claim 1. Similarly, the Examiner offered no indication where claims 1-27 of the '291 patent teach or suggest that a nuclear transcription factor ligand can modulate estrogen activation at an AP-1 site.

Stating that the cells of the '291 patent can be used for comparison to detect responses is at best taking the present inventor's own disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." This is an insufficient and improper basis for an obviousness rejection. The Examiner has failed to make his *prima facie* case and, accordingly, the obviousness type double patenting rejection in light of the '291 patent should be withdrawn.

35 U.S.C. §102.

Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,723,291 (Kushner *et al.*). Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Gaub *et al.* (1990) *Cell,* 63: 1267-1276. Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,639,592 (Evans *et al.*). Claims 1-2, 4, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,004,748 (Pfahl *et al.*). Applicants respectfully traverse.

The Examiner is respectfully reminded that anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983). Applicants explain below that the cited references fails to provide all the elements of the presently claimed invention.

U.S. Patent 5,723,291 (Kushner *et al.*).

The 5,723,291 patent fails to disclose a method in which a cell containing a cognate receptor for a nuclear transcription factor ligand is contacted with a nuclear transcription factor. The Examiner asserts that "fos and jun are nuclear receptors and ligands because they are transcription factor sand they bind to each other." Applicants disagree with the Examiner's characterization of either fos or jun as a transcription factor receptor noting that this is not conventional usage of these terms in the art.

Moreover, the presently pending claims expressly recite as discrete elements:

1) a nuclear transcription factor ligand;
2) an estrogen receptor;
3) a cognate receptor for the nuclear transcription factor ligand;
4) fos; and
5) jun.

In view of their recitation as discrete elements, fos and jun are neither "a transcription factor ligand' nor "a receptor for a transcription factor ligand". The '291 patent does not disclose a screening system having all of these elements. Accordingly the '291 patent fails to anticipate the presently claimed invention and the rejection of claims 1-5, 8, and 10-11 under 35 U.S.C. §102(e) should be withdrawn.

U.S. Patent 5,639,592 (Evans *et al.*).

The 5,639,592 patent also fails to disclose a method having all of the elements of the presently claimed methods. As explained above, particularly in view of their recitation as discrete elements, neither fos nor jun is "a transcription factor ligand' or "a receptor for a transcription factor ligand". The '592 patent fails to disclose an assay method in which a cell is contacted with **both** a transcription factor ligand (which is not a fos or jun), and a compound having AP-1 mediated estrogenic activity. Accordingly, the rejection of claims 1-5, 8, and 10-11 under 35 U.S.C. §102(e) in light of the '592 patent should be withdrawn.

U.S. Patent 6,004,748 (Pfahl *et al.*).

The 6,004,748 patent also fails to anticipate the presently pending claims. As explained above, particularly in view of their recitation as discrete elements, neither fos nor jun is "a transcription factor ligand' or "a receptor for a transcription factor ligand". The '748 patent fails to disclose a method that involves contacting a cell with a compound having AP-1 mediated estrogenic activity (*e.g.* β-estradiol) and with a transcription factor ligand (not fos or jun). Lacking such a teaching, the '748 patent fails to provide a limitation of presently pending independent claim 1 or dependent claims 2, 4, 8, and 10-11. The rejection of these claims under 35 U.S.C. §102(e) should therefore be withdrawn.

Gaub *et al.* (1990) *Cell*, 63: 1267-1276.

Gaub *et al.* also fails to anticipate the presently claimed invention. The Examiner is reminded that claim 1 expressly recites:

> a) providing a first cell comprising:
> an estrogen receptor;
> a cognate receptor for said nuclear transcription factor ligand;
> fos;
> jun; and
> a promoter comprising an AP-1 site that regulates expression of a first reporter gene;

Clearly, the cognate receptor is something other than fos or jun. Contrary to the Examiner's assertion, Gaub *et al.* does not teach a cell comprising an estrogen receptor **and** a cognate receptor for said nuclear transcription factor ligand.

As neither jun nor fos are cognate receptors for a nuclear transcription factor ligand the Gaub *et al.* reference fails to disclose a cell comprising both an **estrogen receptor and a cognate receptor** for a transcription factor ligand. Claim 1 is therefore not anticipated by Gaub *et al.* and consequently, dependent claims 2-5, 8, and 10-11, which incorporate all the limitations of claim 1 are also not anticipated. Accordingly the rejection of claims 1-5, 8, and 10-11 under 35 U.S.C. §102(b) in light of Gaub *et al.* should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Should the Examiner consider maintaining his rejections or making new rejections Applicants request a telephone interview with the Examiner and his supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/103,355 WITH ENTRY OF THIS AMENDMENT

In the claims:

1. A method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site, said method comprising the steps of:

a) providing a first cell **[containing]comprising**:

an estrogen receptor**[,];**

a cognate receptor for said nuclear transcription factor ligand**[,];**

fos;

jun; and

a promoter comprising an AP-1 site **[which]that** regulates expression of a first reporter gene;

b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and

c) detecting expression of said first reporter gene, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

10. The method of claim 1, wherein said cell expresses **[an AP-1 protein]said fos or said jun** from a heterologous DNA.

11. The method of claim 10, wherein said AP-1 protein **said fos or said jun** is c-jun.

APPENDIX B

CLAIMS PENDING IN USSN 09/103,355 WITH ENTRY OF THIS AMENDMENT

1. A method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site, said method comprising the steps of:

a) providing a first cell comprising:

an estrogen receptor;

a cognate receptor for said nuclear transcription factor ligand;

fos;

jun; and

a promoter comprising an AP-1 site that regulates expression of a first reporter gene;

b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and

c) detecting expression of said first reporter gene, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

2. The method of claim 1, further comprising the steps of:

d) providing a cell containing an estrogen receptor, a cognate receptor for said nuclear transcription factor ligand, and a promoter comprising an estrogen response element (ERE) that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

3. The method of claim 2, wherein said first cell and the cell containing the estrogen response element that regulates expression of a second reporter gene are the same cell.

4. The method of claim 1, further comprising the steps of:

d) providing a cell containing a cognate receptor of said transcription factor ligand, and a promoter comprising a response element for said cognate receptor that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

5. The method of claim 4, wherein said first cell and the cell containing a cognate receptor of said transcription factor ligand are the same cell.

6. The method of claim 1, wherein said nuclear transcription factor ligand is selected from the group consisting of a glucocorticoid, a progestin, vitamin D, retinoic acid, an androgen, a mineralcorticoid, and a prostangladin..

7. The method of claim 1, wherein said cognate receptor is selected from the group consisting of an estrogen receptor, a glucocorticoid receptor, a progestin PR-A receptor, and progestin PR-B receptor, androgen receptor, a mineralcorticoid receptor, and a prostaglandin receptor.

8. The method of claim 1, wherein said cell expresses said estrogen receptor from a heterologous DNA.

9. The method of claim 1, wherein said cell expresses said cognate receptor from a heterologous DNA.

10. The method of claim 1, wherein said cell expresses said fos or said jun from a heterologous DNA.

11. The method of claim 10, wherein said AP-1 protein said fos or said jun is c-jun.

12. The method of claim 1, wherein said nuclear transcription factor is a progestin; and said cognate receptor is a progestin receptor.

13. The method of claim 1, wherein said nuclear transcription factor is a glucocorticoid and said cognate receptor is a GR receptor.